Leukemia insights

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In this month's Leukemia Insights newsletter, written by Naveen Pemmaraju, M.D., Lucia Masarova, M.D., and Prithviraj Bose, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we outline clinical trials offered for patients with myeloproliferative neoplasms. Learn more about our Leukemia program.

Clinical trials for patients with myelofibrosis: Established approaches and new paradigms

It is an exciting time in myelofibrosis research. A plethora of new therapeutic targets have emerged in recent years as the underlying biology of the disease continues to be unraveled. The first results from two phase 3 studies in the frontline setting were presented at the 2023 ASH Annual meeting. While JAK inhibitor-based combinations are mechanism-based, synergistic and potentially disease-modifying, one lesson learned from these trials was that it may be difficult to improve disease-related symptoms with the use of rational combinations over what is achieved by ruxolitinib alone. Along these same lines, there is the realization in the field that it may be time to rethink traditional endpoints (spleen and symptom improvement) in myelofibrosis registration trials, especially as the field moves beyond JAK inhibition. Already, some phase 3 trials are using RBC transfusion independence and overall survival as primary endpoints. It is likely that this area will continue to evolve over time. Below is a summary of clinical trials available to patients with MF at MD Anderson at present and in the near future.

Trials in the upfront (JAK inhibitor-naïve) setting:

1. *Selinexor.* Selinexor is a selective inhibitor of nuclear export (SINE) approved for use in patients with multiple myeloma and certain forms of non-Hodgkin's lymphoma. This agent is now being studied in combination with ruxolitinib in JAK inhibitor-naïve patients with MF in the phase 3 portion of the XPORT-034 trial at a dose of 60 mg once weekly, significantly lower than in other indications. Results in 24 patients participating in the phase 1 portion of this trial provided the impetus to study this synergistic combination in the frontline setting, with rates of SVR35 and TSS50 of 79% and 58%, respectively, at 24 weeks, at this dose of selinexor in combination with ruxolitinib. This trial is about to open at MD Anderson; Dr. Bose is PI. Learn about the trial.

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2. Zilurgisertib. Zilurgisertib is a potent, small-molecule inhibitor of ACVR1/ALK2, the mechanism believed to underlie the anemia benefits of momelotinib and pacritinib. Inhibition of ACVR1/ALK2 leads to down-regulation of hepcidin and increases availability of iron for erythropoiesis. Results with this agent thus far in the public domain pertain to its use as monotherapy for anemia of MF and in "add on" fashion in anemic patients on a stable dose of ruxolitinib. The trial now has an open cohort for previously untreated anemic patients with MF who receive the combination of zilurgisertib and ruxolitinib from the outset. Dr. Bose is PI. for anemia of MF and in "add on" fashion in anemic patients on a stable dose of ruxolitinib. The trial now has an open cohort for previously untreated anemic patients with MF who receive the combination of zilurgisertib and ruxolitinib from the outset. Dr. Bose is PI. Learn about the trial.

Trials in the "add on" setting:

1. *Zilurgisertib.* As alluded to above, the ACVR1/ALK2 inhibitor zilurgisertib has been studied, both alone and as an "add on" in anemic patients with MF on a stable dose of ruxolitinib. Dose-dependent down-regulation of hepcidin has been demonstrated, and anemia responses observed in both the monotherapy and "add on" settings. This trial is open to accrual. Dr. Bose is PI. Learn about the trial.
2. *INCB057643* . INCB057643 is an orally administered bromodomain and extra-terminal (BET) protein inhibitor. BET proteins control the transcription of numerous proteins key to MF pathophysiology, e.g., nuclear factor kappa B, c-Myc and members of the B-cell lymphoma 2 (Bcl2) family, and synergism between JAK and BET inhibitors has been demonstrated in preclinical models. This agent is being studied in "add on" fashion in patients on a stable dose of ruxolitinib with an insufficient response and early evidence of clinical activity (SVR35, TSS50) has been demonstrated. This trial is recruiting participants. Dr. Bose is PI. Learn about the trial.
3. *CK0804*. CK0804 is an umbilical cord blood-derived regulatory T-cell product. It is being studied in the "add on" setting in patients on a stable dose of ruxolitinib who have palpable splenomegaly, symptoms or cytopenias. CK0804 is infused every 28 days for up to 6 cycles. Preliminary data show safety, as well as promising clinical activity. This trial is open to accrual. Dr. Masarova is PI. Learn about the trial.
4. *Tasquinimod.* Tasquinimod is an inhibitor of histone deacetylase 4 (HDAC4) and the alarmins A8 and A9. It inhibits the immunosuppressive effects of mesenchymal stromal cells and myeloid derived suppressor cells on the bone marrow microenvironment, with the goal of improving inflammation and fibrosis. It will be studied both as monotherapy (in patients with disease relapsed/refractory to JAK inhibitor therapy and in those who are intolerant to approved JAK inhibitors), and in "add on" fashion in patients with an insufficient response to ruxolitinib who are on a stable dose of the latter. In addition to the typical criteria for suboptimal response to ruxolitinib, which tend to be based on splenomegaly and symptoms, this soon-to-open trial (NCT06327100) will also consider progressive cytopenias for eligibility. Dr. Masarova is PI.

Trials for patients failing JAK inhibitor therapy:

1. *TP-3654.* TP-3654 is an orally bioavailable PIM kinase inhibitor that is selective for PIM1, thus minimizing myelosuppression. This drug is currently being studied in a phase 1/2 trial in patients who have previously received or are ineligible for JAK inhibitor therapy. A baseline platelet count as low as 25 x 10^9 /L is permitted. Early results show striking symptom responses correlating with cytokine down-regulation, as well as some spleen responses. This trial is currently enrolling patients. Dr. Bose is PI. Learn about the trial.
2. *Imetelstat.* Imetelstat is a telomerase inhibitor that, in a phase 2 study of 2 different doses in patients whose disease had failed JAK inhibitor therapy, yielded a median overall survival of 29.9 months when administered at a dose of 9.4 mg/kg IV every 3 weeks. Median survival in this setting has been reported by several groups to be in the range of 11-14 months. Reductions in bone marrow fibrosis grade and driver mutation variant allele frequency were reported in over 40% of patients at this dose. This agent is being studied against physician's choice of standard therapy (excluding JAK inhibitors) in a global, phase 3, pivotal randomized controlled trial (IMpactMF) in patients whose disease has failed JAK inhibitor therapy. This trial is enrolling patients. Dr. Bose is PI.
3. *INCB057643.* As discussed above, INCB057643 is a BET inhibitor administered daily continuously. Besides the "add on" approach discussed above, the agent is also being studied as monotherapy for patients with relapsed/refractory MF in a separate cohort of the same trial. Early evidence of clinical activity as a single agent has been demonstrated. Dosing differs by baseline platelet count. The trial is open to accrual. Dr. Bose is PI. Learn about the trial.
4. *Tasquinimod.* As discussed above, tasquinimod is an inhibitor of histone deacetylase 4 (HDAC4) and the alarmins A8 and A9. It will be studied as monotherapy in patients with disease relapsed/refractory to JAK inhibitor therapy and in those who are intolerant to approved JAK inhibitors. There will also be an "add on" cohort for patients with an insufficient response to ruxolitinib who are on a stable dose of the latter. The trial (NCT06327100) will open soon. Dr. Masarova is PI.
5. *EP31670*. This is an oral dual inhibitor of BET family proteins and the histone acetyltransferase (HAT), p300. Myeloid malignancies enriched for *ASXL1* mutations may be particularly sensitive to this novel agent. *ASXL1* is the most common non-driver gene mutated in patients with MF. Patients with intermediate- or high-risk MF who have previously received at least one JAK inhibitor or are not candidates for JAK inhibitors are eligible. The trial (NCT054885480) also enrolls patients with other relapsed/refractory myeloid malignancies. The drug is administered orally for 2 weeks on a 4-week cycle. The trial allows both monotherapy and "add on" to a stable dose of a JAK inhibitor. This trial is open. Dr. Borthakur is PI.

Trials for anemia:

1. *Zilurgisertib* . As discussed above, this agent is an orally administered inhibitor of ACVR1/ALK2 that improves anemia via down-regulation of hepcidin and improved utilization of iron for erythropoiesis. It is being studied both as monotherapy and in "add on" fashion in patients who are on a

stable dose of ruxolitinib. Patients may be RBC transfusion-dependent or just anemic. Dose-dependent decreases in serum hepcidin and clinical anemia responses have been observed, in both the monotherapy and "add on" cohorts. The trial is recruiting participants. Dr. Bose is PI. Learn about the trial.

1. *DISC-0974.* DISC-0974 is a monoclonal antibody against hemojuvelin, a positive regulator of hepcidin. This thus represents a different mechanism of pharmacologic down-regulation of hepcidin than ACVR1/ALK2 inhibition. DISC-0974 can be administered alone, or added to a stable dose of a JAK inhibitor (other than Momelotinib). Early clinical data are promising. This trial is open to accrual. Dr. Bose is PI. Learn about the trial.

Anti-fibrotic agents:

1. *Elotuzumab.* The fibrocytes that engender bone marrow fibrosis in MF have been shown to be clonal and monocyte-derived. SLAMF7 has been demonstrated to be a therapeutic target on circulating monocytes that are the precursors of fibrocytes. Elotuzumab is a monoclonal antibody against SLAMF7 that is approved for the treatment of multiple myeloma in conjunction with with IMiDs® and dexamethasone. In this investigator-initiated trial, elotuzumab monotherapy is being studied in patients who are not JAK inhibitor candidates. Prior JAK inhibitor therapy is allowed. Symptom, anemia and platelet responses, as well as reductions in bone marrow fibrosis grade, have been observed. This trial is open to accrual. Dr. Bose is PI. Learn about the trial.

2. *PXS-5505* . Lysyl oxidase-like 2 (LOXL2) is an extracellular matrix enzyme involved in fibrogenesis in patients with MF via facilitation of collagen and elastin cross-linking. PXS-5505 is a pan-LOX inhibitor administered orally twice daily. It is being studied in patients with MF with disease relapsed/refractory to, or who are ineligible for/intolerant of JAK inhibitors. Early data show excellent target inhibition, safety and improvement in collagen fibrosis with stable to improved blood counts. This trial is recruiting participants. Dr. Masarova is PI. Learn about the trial.

Targeting mutant calreticulin:

The unique biology of mutant calreticulin lends itself to immunotherapeutic approaches. *CALR* deletions and insertions in exon 9, seen in 20-30% of patients with primary and post-essential thrombocythemia (ET) MF, affect the C-terminal of the chaperone protein, leading to a loss of negative charge and loss of calcium binding. Importantly, mutant calreticulin loses its endoplasmic reticulum retention motif and is secreted extracellularly, where it binds to the thrombopoietin receptor, MPL, to exert its oncogenic effect.

1. *INCA033989*. This is a fully human, IgG1 monoclonal antibody against mutant calreticulin being studied in a global phase 1 trial with dose escalation and expansion phases (NCT05936359). Patients with *CALR*-mutant MF must have previously been treated with a JAK inhibitor and have relapsed/refractory disease or be intolerant, and ineligible for other JAK inhibitors. Splenomegaly, disease-related symptoms and platelets >50 x 10^9/L are required. The trial also features a *CALR* -mutant ET cohort. The antibody is given IV every 2 weeks. This trial will open soon. Dr. Masarova is PI.
2. *JNJ*-88549968. This phase 1, first-in-human clinical trial (NCT06150157)

2. features a T-cell redirecting bispecific (CD3 x mutant CALR) antibody, administered subcutaneously in patients with MPNs with *CALR* mutations. The study will initially focus on patients with *CALR*-mutated myelofibrosis post one prior therapy, then expanding to patients with *CALR* -mutated ET. This study, which has dose escalation and expansion phases, is enrolling patients. Dr. Pemmaraju is PI.
3. *VAC85135MPN10001.* This is a novel vaccine from Janssen that is being studied (NCT05444530) in patients with *CALR*- or *JAK2*-mutated patients with ET or MF in combination with either 1 mg/kg or 3 mg/kg of ipilimumab (to augment T-cell responses). Both type 1/type 1-like and type 2/type 2-like *CALR* mutations are permissible. This is a finite duration therapy. Interestingly, the study also enrolls patients with *JAK2* -mutated disease, but they must be of a certain HLA type. Prior JAK2 inhibitor therapy is not permitted, but prior interferon is. Dr. Bose is PI.